ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lysodren 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of mitotane.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, biconvex, round, scored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma.
The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.

4.2 Posology and method of administration

Treatment should be initiated and followed by a suitably experienced specialist.

Dose adjustment is aimed to reach a therapeutic window (mitotane plasma levels between 14 and 20 mg/L) which ensures optimal use of Lysodren with acceptable safety. Indeed neurologic toxicity has been associated with levels above 20 mg/L and therefore this threshold should not be reached. Weaker evidence has suggested that mitotane plasma levels above 14 mg/L may result in enhanced efficacy. Thus,mitotane plasma levels should therefore be monitored in order to adjust the Lysodren dose and avoiding reaching toxic levels.

It is advised to perform mitotane plasma assays after each dose change and at frequent (e.g. biweekly) intervals until optimal maintenance dose is reached. In dose readjustments it should be taken into account that adjustments do not produce immediate changes in plasma levels of mitotane (section 4.4). In addition, because of tissue accumulation, monitoring of mitotane plasma level must be pursued regularly (e.g. monthly) once maintenance dose has been reached.
Regular monitoring (e.g.: bimonthly) of mitotane plasma levels is also necessary after interruption. Treatment can be resumed when mitotane plasma levels will be ranged between 14 and 20 mg/L. Due to the prolonged half-life, significant serum concentrations may persist for weeks after cessation of therapy.

Adult patients
Treatment should be started with 2-3 g of Lysodren per day and increased stepwise until mitotane plasma level reaches the therapeutic window with acceptable safety, which usually corresponds to a cumulative dose of 75 g . The total daily dose may be divided in two or three doses according to patient's convenience, and the treatment should be preferably taken during meals (see section 4.5).

In some patients in whom it is urgent to control Cushing's symptoms, the starting dose of Lysodren could be as high as 4-6 g daily in divided doses until a cumulative dose of 75 g is reached (in approximately 15 days). In this case, mitotane plasma levels should be closely monitored (e.g. once a week). It is generally not recommended to exceed 6g/day.

If serious adverse reactions occur, such as neurotoxicity, treatment with mitotane may need to be transiently interrupted. In case of mild toxicity, dosage should be reduced until the maximum tolerated dosage is attained.

Treatment with Lysodren should be continued as long as clinical benefits are observed. If no clinical benefits are observed after 3 months at optimal dose, treatment should be discontinued.

Paediatric patients
The safety and efficacy of mitotane in patients under the age of 18 years have not been established and, at present only very limited data are available in this age group.

The paediatric dosage of mitotane has not been well characterised but appears equivalent to that of adults: treatment should be initiated at 1.5 to 3.5 g/m^2/day in children and adolescents and may be reduced after 2 or 3 months according to the mitotane plasma levels. Doses should be reduced in case of serious toxicity as in adults (see above).

The total daily dose may be divided in two or three doses according to patient's convenience, and it should be preferably taken during meals.

Liver impairment
Since mitotane is mainly metabolised through the liver, mitotane plasma levels are expected to increase if liver function is impaired. There is no experience in the use of mitotane in patients with hepatic impairment, so data are insufficient to give a dose recommendation in this group. Until further data are available, the use of mitotane in patients with severe hepatic impairment is not recommended and, in cases of mild to moderate hepatic impairment, caution should be exercised. Monitoring of mitotane plasma levels is specially recommended in these patients (see section 4.4).

Renal impairment
There is no experience in the use of mitotane in patients with renal impairment, so data are insufficient to give a dose recommendation in this group. Until further data are available, the use of mitotane in patients with severe renal impairment is not recommended and, in cases of mild to moderate renal impairment, caution should be exercised. Monitoring of mitotane plasma levels is specially recommended in these patients (see section 4.4).

Elderly patients
There is no experience on the use of mitotane in elderly patients, so data are insufficient to give a dose recommendation in this group. Until further data are available caution should be exercised and frequent monitoring of mitotane plasma levels is highly recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Breast-feeding is contra-indicated while taking mitotane. The prolonged elimination of mitotane from the body after discontinuation of Lysodren should be considered (see section 4.6).

Lysodren and spironolactone must not be used concomitantly (see section 4.5).

4.4 Special warnings and special precautions for use

Before the initiation of the treatment: All possible tumour tissues should be surgically removed from large metastatic masses before mitotane administration is instituted. This is necessary to minimise the possibility of infarction and haemorrhage in the tumour due to a rapid cytotoxic effect of mitotane.

Shock, severe trauma or infection: Mitotane should be temporarily discontinued immediately following shock, severe trauma or infection, since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances, since the depressed adrenal gland may not

immediately start to secrete steroids. Because of an increased risk of acute adrenocortical insufficiency, patients should be instructed to contact their physician immediately if injury, infection, or other illness occurs. Patients should carry with them the card provided with the package leaflet indicating that they are prone to adrenal insufficiency and that in case of emergency care, adequate precautionary measures should be taken.

Monitoring of plasma levels: Mitotane plasma levels should be monitored in order to adjust the Lysodren dose. It may be especially recommended in cases where administration of higher starting doses is considered necessary (e.g. in highly symptomatic patients) to reach the desired therapeutic levels more rapidly.. The therapeutic window of mitotane lies between 14 mg/l and 20 mg/l. A dose adjustment may be necessary to achieve the correct therapeutic level (see section 4.2) and avoid specific adverse reactions. Mitotane plasma levels higher than 20 mg/l may be associated with severe undesirable effects and offer no further benefit in terms of efficacy.

In patients with severe liver disease or severe renal impairment, there are insufficient data to support the use of mitotane (see section 4.2). In patients with mild or moderate hepatic impairment caution should be exercised and monitoring of liver biochemistry should be performed. In patients with mild or moderate renal impairment caution should be exercised. Monitoring of mitotane plasma levels is particularly recommended in patients with liver impairment and/or renal insufficiency (see section 4.2) for whom treatment with Lysodren is considered necessary.

Mitotane tissue accumulation: Mitotane is stored in fat tissues which serve as reservoirs of the active substance which results in a prolonged half-life. Consequently, despite a constant dose, mitotane levels may increase. Therefore, monitoring of mitotane plasma levels (e.g.: bimonthly) is also necessary after interruption of treatment. In addition, caution should be taken when treating overweight patients as prolonged release of mitotane can occur and close monitoring of mitotane plasma levels is therefore highly recommended.

Central nervous system disorders: Long-term continuous administration of high doses of mitotane may lead to reversible brain damage and impairment of function. Behavioural and neurological assessments should be made at regular intervals especially when mitotane plasma levels exceed 20 mg/l (see section 4.8).

Risk of adrenal insufficiency: A substantial percentage of patients treated show signs of adrenal insufficiency. Therefore steroid replacement may be necessary in these patients. Since mitotane increases plasma levels of steroid binding proteins, free cortisol and corticotropin (ACTH) determinations are necessary for optimal dosing of steroid substitution (see section 4.8).

Women of childbearing potential: Women of childbearing potential have to use effective contraception during treatment with mitotane (see section 4.6).

Bleeding time: Prolonged bleeding time has been reported in patients treated with mitotane and this should be taken into account when surgery is considered (see section 4.8).

Warfarin and coumarin-like anticoagulants: physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering mitotane to patients on coumarin-like anticoagulants (see section 4.5).

Mitotane is a hepatic enzyme inducer and it should be used with caution in case of concomitant use of medicinal products influenced by hepatic enzyme induction (see section 4.5).

Paediatric population: In children, neuro-psychological retardation can be observed during mitotane treatment. In such cases, thyroid function should be investigated in order to identify a possible thyroid impairment linked to mitotane treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Spironolactone: Mitotane should not be given in combination with spironolactone since this medicinal product may block the action of mitotane (see section 4.3).

Warfarin and coumarin-like anticoagulants: Mitotane has been reported to accelerate the metabolism of warfarin by the mechanism of hepatic microsomal enzyme induction, leading to an increase in dosage requirements for warfarin. Therefore, physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering mitotane to patients on coumarin-like anticoagulants.

Substances metabolised through cytochrome P450: Mitotane has been shown to have an inductive effect on cytochrome P450 enzymes. Therefore the plasma concentrations of the products metabolised via cytochrome P450 may be modified. In the absence of information on the specific P450 isoenzymes involved, caution should be taken when coprescribing active substances metabolised by this route such as, among others, anticonvulsants, rifabutin, rifampicin, griseofulvin and St. John's Wort (*Hypericum perforatum*).

Medicinal products active on central nervous system: Mitotane can give rise to central nervous system undesirable effects at high concentrations (see section 4.8). Although no specific information on pharmacodynamic interactions in the central nervous system is available, this should be borne in mind when co-prescribing medicinal products with central nervous system depressant action.

Food and oil: Data with various mitotane formulations suggest that administration with food and/or oil enhance absorption (see section 5.2).

Hormone binding protein: Mitotane has been shown to increase plasma hormone binding protein: this should be taken into account when interpreting the results of hormonal assays.

4.6 Pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate adverse reactions of mitotane on the health of the foetus. Animal reproduction studies have not been conducted with mitotane. Animal studies with similar substances have shown reproductive toxicity (see section 5.3). Lysodren should be given to a pregnant woman only if clearly needed and if the clinical benefit clearly outweighs any potential risk to the foetus.

Women of childbearing potential have to use effective contraception during treatment. The prolonged elimination of mitotane from the body after discontinuation of Lysodren should be considered.

Lactation

Due to the lipophilic nature of mitotane, it is likely to be excreted in breast milk. Breastfeeding is contra-indicated while taking mitotane (see section 4.3). A decision should be made whether to discontinue breast-feeding or to discontinue Lysodren taking into account, on an individual basis, the importance of the treatment to the mother.
The prolonged elimination of mitotane from the body after discontinuation of Lysodren should be considered.

4.7 Effects on ability to drive and use machines

Lysodren has a major influence on the ability to drive and use machines. Since sedation, lethargy, vertigo, and other central nervous system undesirable effects can occur, ambulatory patients should be cautioned about driving, operating machines, and other hazardous pursuits requiring mental and physical alertness.

4.8 Undesirable effects

More than 80 % of patients treated with mitotane have shown at least one type of undesirable effect. The main types of adverse reactions, presented in order of decreasing seriousness, consist of the following:

System Organ Class	**Undesirable effect (frequency)** ***Very common (≥ 1/10)***	***Common (≥1/100 , <1/10*)**	***Rare (≥1/10,000, <1/1,000) or very rare (<1/10,000), including isolated reports***
Infections and infestations			Opportunistic mycoses
Blood and lymphatic system disorders	Leucopoenia Bleeding time prolonged	Thrombocytopenia Anaemia	
Metabolism and nutrition disorders	Hypercholesterolemia Hypertriglyceridaemia		Hypouricaemia
Nervous system and psychiatric disorders	Ataxia Confusion Myasthenia Paresthesia Anorexia Asthenia Vertigo Sleepiness	Polyneuropathy Mental impairment Movement disorder Dizziness Headache	
Eye disorders			Maculopathy Retinal toxicity Diplopia Lens opacity Visual impairment Vision blurred
Cardiac and vascular disorders			Hypertension Orthostatic hypotension Flushing
Gastrointestinal disorders	Vomiting Diarrhoea Mucositis Nausea Epigastric discomfort		Salivary hypersecretion
Hepato-biliary disorders			Liver damage (hepatocellular/cholestatic /mixed)
Skin and subcutaneous tissue disorders	Skin rash		
Renal and urinary disorders			Haemorrhagic cystitis Haematuria Proteinuria
Reproductive system and breast disorders	Gynaecomastia		

General disorders and administration site conditions			Hyperpyrexia
Investigations	Plasma cholesterol increased Plasma triglycerides increased Elevated liver enzymes		Blood uric acid decreased

• Gastrointestinal disorders are the most frequently reported (10 to 100 % of patients) and are reversible when the dose is reduced. Some of these effects (anorexia) may constitute the hallmark of initial central nervous system impairment.

• Nervous system undesirable effects occur in approximately 40 % of the patients. Other undesirable central nervous effects have been reported in literature such as memory defects, aggressiveness, central vestibular syndrome, dysarthria, or Parkinson syndrome. Serious undesirable effects appear linked to the cumulative exposure to mitotane and are most likely to occur when mitotane plasma levels are at 20 mg/l or above. At high doses and after prolonged utilization, brain function impairment can occur. Nervous system undesirable effects appear reversible after cessation of mitotane treatment and decrease in plasma levels (see section 4.4).

• Metabolic disorders such as increases in plasma cholesterol or triglycerides are very common.

• Skin rashes which have been reported in 5 to 25 % of the cases do not seem to be dose related.

• Leucopenia has been reported in 8 to 12 % of patients. Prolonged bleeding time appears a frequent finding (90 percent of the cases): although the exact mechanism of such an effect is unknown and its relation with mitotane or with the underlying disease is uncertain, it should be taken into account when surgery is considered.

• The activity of liver enzymes (gamma-GT, aminotransferase, alkaline phosphatase) is commonly increased. Autoimmune hepatitis has been reported in 7 % of patients with no other information on mechanism. Liver enzymes normalize when the mitotane dose is decreased. A case of cholestatic hepatitis has been reported. Therefore, the possibility of mitotane-induced liver damage cannot be excluded.

• Other isolated undesirable effects have been reported involving: the eye (visual impairment, maculopathy, vision blurred, diplopia, lens opacity, retinal toxicity); the renal and urinary system (haematuria, haemorrhagic cystitis, proteinuria); cardiovascular system (hypertension, or orthostatic hypotension, and flushing); and some miscellaneous effects including generalized aching; hyperpyrexia; decreased plasma uric acid.

• Because of its adrenolytic activity and its action on cortisol metabolism, mitotane treatment induces a state of functional adrenal insufficiency, which necessitates hormone supplementation. Since mitotane increases plasma level of steroid binding proteins, free cortisol and ACTH determinations are necessary for optimal dosing of steroid substitution (see section 4.4).

In paediatric patients:
Nervous system disorders: neuro-psychological retardation may be observed during mitotane treatment. In such cases, thyroid function should be investigated in order to identify a possible thyroid impairment linked to mitotane treatment.

Hypothyroidism and growth retardation may be also observed during mitotane treatment.

4.9 Overdose

Mitotane overdose may lead to central nervous system impairment especially if mitotane plasma levels are above 20 mg/l. No proven antidotes have been established for mitotane overdose. The patient should be followed closely, taking into account that impairment is reversible but given the long half-life and the lipophilic nature of mitotane it may take weeks to return to normal. Other effects should be treated symptomatically. Because of its lipophilic nature, mitotane is not likely to be dialysable.
It is recommended to increase frequency of mitotane plasma level monitoring (e.g. biweekly) in patients at risk of overdose (e.g. in case of renal or hepatic impairment, obese patients or patients with a recent weight loss).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents. ATC code: L01XX23

Mitotane is an adrenal cytotoxic active substance, although it can cause adrenal inhibition, apparently without cellular destruction. Its biochemical mechanism of action is unknown. Data are available to suggest that mitotane modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex. The administration of mitotane alters the extra-adrenal metabolism of cortisol in man, leading to a reduction in measurable 17-hydroxy corticosteroids, even though plasma levels of corticosteroids do not fall. Mitotane apparently causes increased formation of 6-beta-hydroxyl cholesterol.

Mitotane has not been studied in a clinical therapeutic program. Available clinical information comes mainly from published data in patients with inoperable or metastatic adrenal carcinoma. In terms of overall survival, four studies conclude that mitotane treatment does not increase the survival rate whereas five find an increase in the survival rate. Among the latter, three studies find such an increase only in patients in whom mitotane plasma is above 14 mg/l. In terms of total or partial tumour and/or metastasis regression, eleven studies have shown some degree of improvement and sometimes occasional prolonged remissions. However, in several studies, the objective criteria for evaluating tumour response are missing or not reported. There are nevertheless some studies which provide accurate information on tumour regression or disappearance and demonstrate that the threshold of 14 mg/l appears necessary to induce an objective tumour regression. In addition, mitotane induces a state of adrenal insufficiency which leads to the disappearance of Cushing syndrome in patients with secreting adrenal carcinoma and necessitates substitution hormonotherapy.

Paediatric population: clinical information comes mainly from a large retrospective trial in children (median age, 4 years) who had an unresectable primary tumour or who presented a tumour recurrence or a metastasic disease; most of the children (75%) presented with endocrine symptoms.
Mitotane was given alone or combined with chemotherapy with various agents. Overall, the disease-free interval was 7 months (2 to 16 months). There were recurrences in 40% of children; the survival rate at 5 years was 49%.

The observed undesirable effects were almost comparable to those in adults; however, neuro-psychological retardation, hypothyroidism and growth retardation can also be observed.

5.2 Pharmacokinetic properties

In a study performed in patients with adrenal carcinoma treated with 2 to 3 g daily of mitotane, a highly significant correlation was found between plasma mitotane concentration and the total mitotane dose. The target plasma mitotane concentration (14 mg/l) was reached in all patients within 3 to 5 months and the total Lysodren dose ranged between 283 and 387 g x days of treatment (median value: 363 g x days of treatment). The threshold of 20 mg/l was reached for cumulative amounts of mitotane

of approximately 500 g. In another study, 3 patients with adrenal carcinoma received Lysodren according to a precise protocol allowing fast introduction of a high dose if the product was well tolerated: 3 g (as 3 intakes) on day 1, 4.5 g on day 2, 6 g on day 3, 7.5 g on day 4 and 9 g on day 5. This dose of Lysodren was continued or decreased in function of side effects and plasma mitotane levels. There was a positive linear correlation between the cumulative dose of Lysodren and the plasma levels of mitotane. In two of the 3 patients, plasma levels of more than 14 mg/l were achieved within 15 days and in one of them levels above 20 mg/l were achieved within approximately 30 days. In addition, in both studies, in some patients, the plasma mitotane levels continued to rise despite maintenance or a decrease of the daily dose of mitotane.

Administration of Lysodren tablets with food increased absorption (see section 4.2), although no quantitative measure of relative bioavailability was made.

Autopsy data from patients show that mitotane is found in most tissues of the body, with fat as the primary site of storage.

Metabolism studies in man have identified the corresponding acid, *o,p'*-DDA, as the major circulating metabolite, together with smaller quantities of the *o,p'*-DDE analogue of mitotane. No unchanged mitotane has been found in bile or in urine, where *o,p'*-DDA predominates, together with several of its hydroxylated derivatives.

After intravenous administration, 25% of the dose was excreted as metabolite within 24 hours. Following discontinuation of mitotane treatment, it is slowly released from storage sites in fat, leading to reported terminal plasma half-lives ranging from 18 to 159 days.

For induction with cytochrome P450, see section 4.5.

5.3 Preclinical safety data

Non-clinical data on the general toxicity of mitotane is limited. Reproductive toxicity studies have not been performed with mitotane. However, DDT and other polychlorinated biphenyl analogues are recognised to have deleterious effects on fertility, pregnancy and development, and mitotane could be expected to share these properties. The genotoxic and carcinogenic potential of mitotane have not been investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Microcrystalline cellulose (E 460)
Macrogol 3350
Anhydrous colloidal silica.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After opening: 1 year.

6.4 Special precautions for storage

Store in the original container.

6.5 Nature and contents of container

Square opaque white HDPE bottle containing 100 tablets. Packs of 1 bottle.

6.6 Special precautions for disposal and other handling

This medicinal product should not be handled by persons other than the patient and his/her caregivers and especially not by pregnant women. Caregivers should wear disposable gloves when handling the tablets.

Do not use any tablet which shows signs of deterioration; these should be disposed of in accordance with local requirements.

Unused containers or partially empty bottles should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratoire HRA Pharma
15 rue Béranger
75003 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/273/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/04/2004

10. DATE OF REVISION OF THE TEXT

23/03/2007

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.p.A.
Via del Murillo Km. 2.800
04010 Sermoneta (Latina)
Italy

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lysodren 500 mg tablets
Mitotane

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 500 mg of mitotane.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.
Bottle of 100 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet carefully before opening the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP :

After opening: 1 year

9. SPECIAL STORAGE CONDITIONS

Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused containers or partially empty bottles should be disposed of in accordance with local requirements

11. NAME AND ADDRESS OF THE MARKETING AUTORISATION HOLDER

Laboratoire HRA Pharma
15 rue Béranger
75003 Paris
France

12. MARKETING AUTORISATION NUMBER

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

Lysodren

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lysodren 500 mg tablets
Mitotane

Oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet carefully before opening the bottle.

3. EXPIRY DATE

EXP:

After opening: 1 year

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 tablets.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Lysodren 500 mg tablets
Mitotane

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

A Lysodren patient card is included at the end of this leaflet. You should carefully complete it, cut it out and keep it with you in all cases.

1. WHAT LYSODREN IS AND WHAT IT IS USED FOR

Lysodren is an antitumoral medicine.

This medicine is used for the treatment of symptoms of advanced non operable, secondary localised or recurrent malignant tumour of adrenal glands.

2. BEFORE YOU TAKE LYSODREN

Do not take Lysodren

- If you are allergic (hypersensitive) to mitotane or any of the other ingredients of Lysodren
- If you are breast-feeding (see “Breast-feeding”)
- If you are currently treated with spironolactone (a medicine often used in the treatment of cardiac, hepatic or renal diseases). You should check with your doctor whether or not you are taking spironolactone (see "Taking other medicines").

Take special care with Lysodren

Due to the effects of Lysodren, your doctor may prescribe you some hormonal treatment (steroids) while you are taking Lysodren.

- If you have an injury, an infection or if you are ill, you should immediately contact your doctor.

- In case of shock, severe trauma or infection., your doctor may decide to temporarily stop Lysodren. **Always keep with you the Lysodren patient card that is at the end of this leaflet.**

- if you have severe hepatic or kidney disease, tell it to your doctor. Lysodren may not be suitable for you.

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Lysodren should not be given in combination with spironolactone (a medicine often used in the treatment of cardiac, hepatic or renal diseases (see "Do not take Lysodren").

Lysodren weakens the effects of a medicine named warfarin (this medicine is a blood thinner, a medicine used to prevent blood clots). Therefore, you should always tell your doctor if you take a blood thinner.

Lysodren could interfere with several other medicines such as:
- Medicines used in the treatment of epilepsy (e.g. anticonvulsants).
- Medicines used in the treatment of tuberculosis (e.g. rifabutin or rifampicin).
- Medicines used in the treatment of fungal infections (e.g. griseofulvin)

Lysodren may also interfere with an herbal remedy named St. John's Wort (*Hypericum perforatum*).

Taking Lysodren with food and drink

Lysodren should be preferably taken during meals.

Taking Lysodren with food and/or oil could enhance absorption.

Pregnancy and breast-feeding:

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
In case of pregnancy, your doctor may decide to modify your treatment, as Lysodren may harm the foetus. Therefore, always tell your doctor if you are pregnant or planning to become pregnant.

If you are a woman who may become pregnant, you should use effective contraception during treatment with Lysodren. This is also the case once the treatment is stopped. Lysodren is eliminated very slowly; it may take several months before it disappears from your body. Therefore, after Lysodren is stopped, you should ask your doctor about the use of an effective contraception.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Lysodren while breast-feeding your child. Lysodren is likely to be found in breast milk. Therefore, always tell your doctor if you are breast-feeding or if you are planning to breast-feed your child (see "Do not take Lysodren"). Your doctor will decide to either stop Lysodren or stop breast-feeding.

Driving and using machines

Lysodren has a major influence on your ability to drive and use machines. Therefore, you should ask your doctor about driving, if you have to use machines, or if you are doing some potentially dangerous activities which require mental and physical alertness.

3. HOW TO TAKE LYSODREN

Dosage and Administration

Treatment should be instituted by a suitably experienced specialist until a stable dosage regimen is achieved.

Always take Lysodren exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

In order to find the best dose to treat your disease, your doctor could monitor regularly the quantity of Lysodren you have in your blood.

Adults

At the beginning of the treatment the usual dose is 2-3 g (4 to 6 tablets) of Lysodren per day.
Sometimes, your doctor may start treatment at higher doses such as 4-6 g (8 to 12 tablets).
The total daily dose can be administered in two or three intakes.
The tablets should be swallowed with water and preferably taken during meals.

Tell your doctor or pharmacist if you experience any undesirable effect with Lysodren. Your doctor may decide to stop Lysodren temporarily or to lower the dose if you experience some undesirable effects (especially in the central nervous system).

Children

Very limited data are available on this age group (<18 years).
The daily dose of Lysodren for children will be calculated by your doctor according to the weight and the size of the child. You may administer Lysodren to the child into two or three divided doses at your convenience.

If you take more Lysodren than you should

Please tell your doctor immediately if you have taken accidentally more Lysodren than you should or if a child swallows some and if you or the child experience undesirable effects (central nervous system or digestive undesirable effects).

If you forget to take Lysodren

If you accidentally miss a dose, just take the next dose as normal. Do not take a double dose to make up for the missed one.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lysodren can cause side effects..

If any of the side-effects gets serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or your pharmacist.

A very high percentage of patients treated with Lysodren have experienced some undesirable effects while they were taking Lysodren. These undesirable effects consist mainly of the following:

Very common (≥ 1/10)
For which you should immediately contact your doctor:

- Movement and coordination disorders: confusion, muscle disorders, vertigo, abnormal sensations like pins and needles, feeling sleepy, skin rash

For which you should contact your doctor as soon as possible:
- Vomiting, diarrhoea, nausea, lack of appetite, fatigue

Other very common effects: increase of cholesterol and other lipids in the blood

Common (≥ 1/100 , <1/10)
You should immediately contact your doctor in case of:
- Cutaneous pallor, muscular fatigability, vertigo when standing up, small bruises, nose bleed, dizziness, headache, aggressiveness, difficulties to talk.

Rare (≥ 1/10,000 , <1/1,000) or very rare (<1/10,000) including **isolated reports**
You should immediately contact your doctor in case of:
Fever, infection, visual impairment, vision blurred, double vision, yellowing of the skin and eyes, itching , dark coloured urine, urinary bleeding

Other rare or very rare effects: high or low blood pressure, sensation of warmth of the face decreased plasma uric acid

Some symptoms may reveal complications for which specific medication could be appropriate:
- Adrenal insufficiency: fatigue, abdominal pain, nausea, vomiting, diarrhoea, confusion
- Anaemia: cutaneous pallor, muscular fatigability, breath disorders, vertigo especially when standing up
- Liver impairment: yellowing of the skin and eyes, itching, nausea, diarrhoea, fatigue, dark coloured urine).

In children:
The following undesirable effects were observed: central nervous system (retardation), thyroid problems and growth retardation.

5. HOW TO STORE LYSODREN

Keep out of the reach and sight of children.

Store in the original container.

Do not use after the expiry date which is stated on the carton and/or on the bottle.

Do not use any tablet which shows signs of deterioration.

Unused or deteriorated tablets must not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines, unused containers or partially empty bottles no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Lysodren contains

- The active substance is Mitotane. Each tablet contains 500 mg of mitotane.
- The other ingredients are maize starch, microcrystalline cellulose (E 460), Macrogol 3350, anhydrous colloidal silica.

What Lysodren looks like and content of the pack

Lysodren is presented in white, biconvex, round, scored tablets.
This medicine is available in bottles of 100 tablets.

Marketing Authorisation Holder:

Laboratoire HRA Pharma
15 rue Béranger
F - 75003 Paris
France

Manufacturer:

Bristol-Myers Squibb S.p.A.**,**
Via del Murillo Km. 2.800
I - 04010 Sermoneta (LT)
Italy

This leaflet was approved in 03/2007

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LYSODREN PATIENT CARD

I am on Lysodren (mitotane) treatment **I am prone to acute adrenal insufficiency** **In case I need emergency care, adequate precautionary measures should be taken**	**The name of my Doctor is:** **……………………………………….. Phone: ……………………………….** **For information on the product, please contact:** ***Laboratoire HRA Pharma*** ***Tel: + 33 1 40 33 11 30*** ***lysodren@hra-pharma.com***